IDENTIFICATION OF DRUG DRUG INTERACTION AND MODIFICATION OF PRESCRIPTIONS IN HOSPITALIZED GERIATRIC PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

In

PHARMACY PRACTICE

By

Reg. No: 26113482

DEPARTMENT OF PHARMACY PRACTICE

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD, THASILDAR NAGAR,

MADURAI – 625020.

OCTOBER 2013

DECLARATION

I hereby declare that this thesis work entitled **"IDENTIFICATION OF DRUG DRUG INTERACTION AND MODIFICATION OF PRESCRIPTIONS IN HOSPITALIZED GERIATRIC PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmacy practice ,Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mr.S.K.Sathish, M.Pharm,** Department of pharmacy practice, Ultra College of Pharmacy, Madurai during the academic year Nov 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associateship, fellowship of any other university or institution.

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CERTIFICATE

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EXAMINERS:

1.

2.

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I sincerely extend my thanks to the Librarian ***Mr. P.Sankar,BA,(Lit),M.L.I.Sc*** *Assistant Librarian* ***Ms.V. Sundhravalli, M.L.I.Sc*** *all the Laboratory staffs in Ultra College of Pharmacy.*

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Lastly I express my heartfelt gratitude to the Almighty God, without whose grace all these efforts would have been in vain.

LIST OF ABBREVIATIONS

SL.NO	ABBREVIATION	EXPANSION
1	DDI	Drug-drug interaction
2	CYP	Cytochrome p isoenzyme
3	NSAID	Non steroidal anti-inflammatory
4	GIT	Gastrointestinal tract
5	OAT	Organic anion transporter
6	ACEI	Angiotensin converting enzyme inhibitor
7	OR	Odds ratio
8	PADIs	Potential adverse drug interactions
9	ADR	Adverse drug reaction
10	BNF	British national formulary
11	MAOI	Mono amine oxidase inhibitor
12	SSRI	Selective serotonin reuptake inhibitor

CONTENTS

PROFORMA

DEMOGRAPHIC DATA
Patient Name: IP No: Date:
Age: Sex:
DISEASE
Diagnosis: Drugs used: Duration of disease: Duration of treatment for the disease: Co- morbidities:
Drug interactions and modifications:

Patient Consent Form

Ms. SURYA SURENDRAN post graduate student of Ultra College of Pharmacy Madurai has made me understand below mentioned points in related to the study **"Identification of drug drug interaction and modification of prescriptions in hospitalized geriatric patients in a tertiary care teaching hospital".**

- The Principal investigator had informed me about the complete description of the study.
- I wholeheartedly without any compulsion agree to give all the relevant data regarding the study.
- I am aware of to opt out this study at any given time without hindrance.
- The data collected should be kept under strict confidentiality.
- I will not be subjected to any harmful tests as a part of this study.
- I need not suffer any economic liabilities for this study.

Above mentioned statements are fully understood and the therefore I am willing to give my consent to participate on this study.

Address of Investigator

SURYA SURENDRAN
II year M.Pharm
Ultra College of pharmacy
Madurai

Patient Name:
Sign:

ERRATA

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INTRODUCTION

Drug drug interactions can be defined as the modifications of the effects of one drug i.e.the object drug by the prior or concomitant administration of another drug i.e the precipitant.It is also defined as a pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone.

There are several incidence that a patient may suffer from more than one disease at a time. Many patients especially the elderly are treated continuously with more than one drug for chronic diseases such as hypertension, heartfailure, osteoarthritis [1].The more drugs people take,the more likely they are to have problems caused by one drug interfering with another drug or disease. Older people particularly have problems with drug response. Their liver and kidneys function less effectively, so drugs that are broken down by the liver or excreted by the kidney tend to accumulate, thus potentially causing problems, During the concomitant usage of multiple drugs, there is possibility of occurrence of drug drug interactions. Even these interactions may be so severe as to cause mortality. By the survey it has concluded that incidence of drug drug interactions may be very high in case of hospitalised patients[2,3,4].

The frequency of adverse drug reactions increases disproportionately with an increase in the number of drugs given to patients[5]. Drug drug interactions are well recognized causes of adverse drug effects. Drug drug interactions are a particularly important type of adverse drug event because they are often predictable based on previous reports, clinical studies, and an understanding of pharmacological principles[7].

Numerous studies have demonstrated that many patients receive multiple drug therapy with agents of recognized potential for interaction. As the number of drugs in a patient receives multiple drug therapeutic regimen increases, the greater is the risk of occurrence of a drug interaction. The growing use of pharmacological agents means that drug interaction are of increasing interest for public health. Monitoring of potential drug interaction may improve the quality of drug prescribing and dispensing and it might form a basis for education focus on appropriate prescribing an important duty and responsibility of pharmacist is to minimize their effect if they occur.[9]

The knowledge of drug interactions may allow early recognition and prevention of adverse consequences. The most comprehensive understanding of clinically important drug interactions can be achieved by combining the knowledge of mechanisms with the recognition of high risk patients and the identification of drugs with a narrow therapeutic index. It is essential for all members in the health profession to be aware about potential drug drug interactions and strategies to overcome them. A concerted effort is required to minimise the problems of drug interactions. Each molecule even at therapeutic dose may have certain side effects, but when given in combination drug might augment or diminish the benefit of the other drugs. Hence ,it is important to discuss about the occurrence and management of potential drug drug interactions and bring awareness amongst the health care professional. Pharmacist being in a competent world can play an active role in the assessment as well as prevention of drug drug interactions[4].

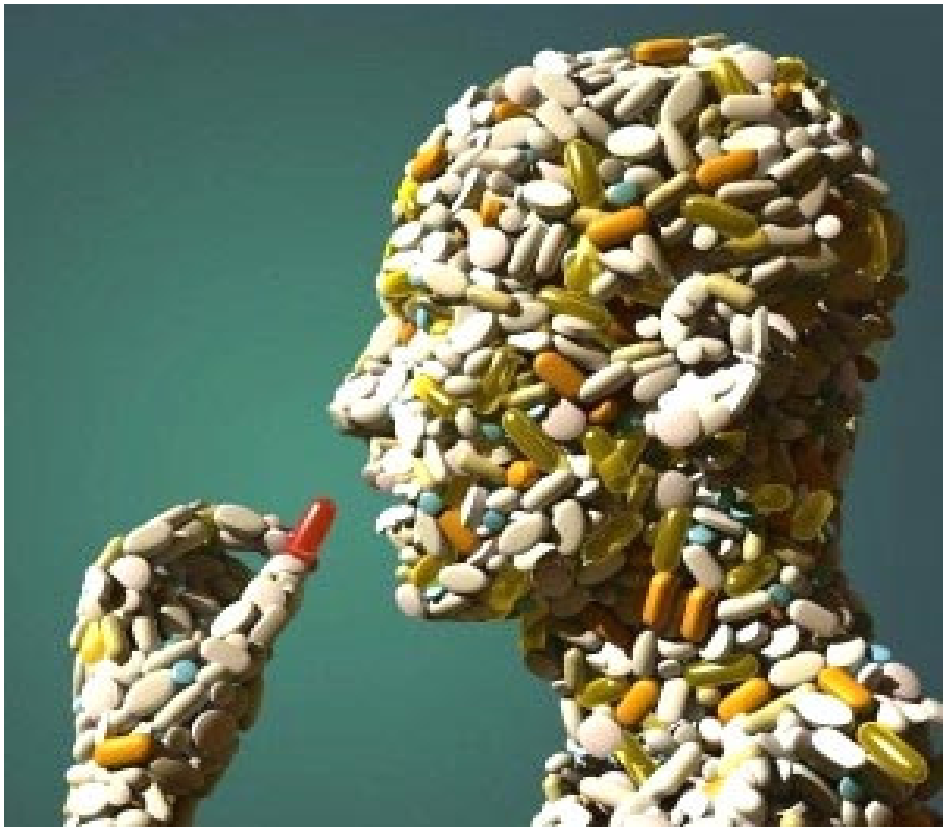
Drug interaction is the pharmacological or clinical response to the administration or co –exposure of a drug with another substance that modifies the patients response to the drug. It is reported that 20-30% of all adverse reactions to drugs are caused by interactions between drugs[10] . This incidence increases among the elderly and patients who take two or more medications.

There are several incidences that a patient may suffer from more than one disease at a time, so it is necessary to treat all these ailments simultaneously. Hence it requires to administer more than one drug at the same time. During the concomitant usage of multiple drugs, there is every possibility of occurrence of drug drug interactions and these interactions may be sometimes so severe to cause mortality[11,12]

Not all drug drug interactions are similar in nature sometimes when two drugs interact , the overall effect of one or both of the drugs may be greater or lesser than desired, e.g. Aspirin in low doses used to prevent platelet aggregation and to prevent clot formation when administered along with oral anticoagulants, aspirin will enhance anticoagulant activity of these but this interaction sometimes leads to dangerous hemarrhoegic condition by causing excessive bleeding.

A drug interaction refers to the possibility that one drug may alter intensity of pharmacological effects of another drug when given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effects that is not seen with either of the drug alone[11] .The most important adverse drug drug interactions occur with drugs that have serious toxicity and a low therapeutic index ,such that relatively small changes in drug level can have significant adverse consequences. Additionally drug drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if under treated[12].

Drug interactions are frequent in medical practice, and their incidence increases with the number of concurrent medications. The elderly are particularly prone to drug interactions,as they are more likely to take more drugs .In addition to age ,other risk factors for drug interactions are malnutrition, malabsorption ,chronic liver disease (including liver metastasis),and impaired renal function[39,40,41]. Pharmacogenetic characteristics of individual patients may also contribute to different drug effects.



Drug combinations with potential to interact are common in medical practice,although their frequency in general medicine has been variable , depending on the patient population, study design, and the screening methods used to identify interactions. In general medical wards, the rate of potential drug interactions has been approximately 60%. Studies conducted in emergency departments found frequencies of potential drug interactions in the range of 16% and 47%[37]. Ambulatory patients with variable clinical conditions who were screened for potential drug interactions by their family physician were found to be exposed to a potential drug interactions by their family physician were found to be exposed to a drug interaction in almost 70% of cases.

Drug interaction is a situation in which a substance affects the activity of drug, when both are administered together.This action can be synergistic or antagonistic (Synergistic means the drugs effect is increased. Antagonistic means the drug effect is decreased) or a new effect can be produced that neither produces on its own. Typically interactions between drugs come to mind.(drug drug interaction).

If a patient is taking two drugs and one of them increases the effect of the other. It is possible that an overdose may occur. The interaction of the two drugs may also increase the risk of that side effects will occur.On the other hand , if the action of a drug is reduced it may cease to have any therapeautic use because of under dosage.

Example; The use of codeine with paracetamol to increase its analgesic effect.

FACTORS AFFECTING DRUG INTERACTIONS

- **Old age;**

Age may affect the interaction of drugs. For example , liver metabolisam,kidney function, nerve transmission or the functioning of bone marrow all decrease with age. In addition in old age there is a sensory decrease that increase the chances of errors being made in the administration of drugs.

- **Polypharmacy;**

The more drugs a patient takes the more likely it will be that some of them will interact.

- **Genetic factors;**

Genes synthesize enzymes that metabolize drugs. Some races have genotypic variations that could decrease or increase the activity of these enzymes. The consequence of this would, on occasions, be a greater predisposition towards drug interactions and therefore a greater predisposition for adverse affects to occur. This is seen in genotype variations in the isoenzymes of cytochrome p450.

- **Hepatic or renal diseases;**

The blood concentrations of drugs that are metabolized in the liver or eliminated by the kidneys may be altered if either of these organs is not functioning correctly. If this is the case an increase in blood concentration is normally seen.

Serious diseases that could worsen if the dose of the medicine is reduced.

- **Drug dependent factors;**

Narrow therapeutic index;

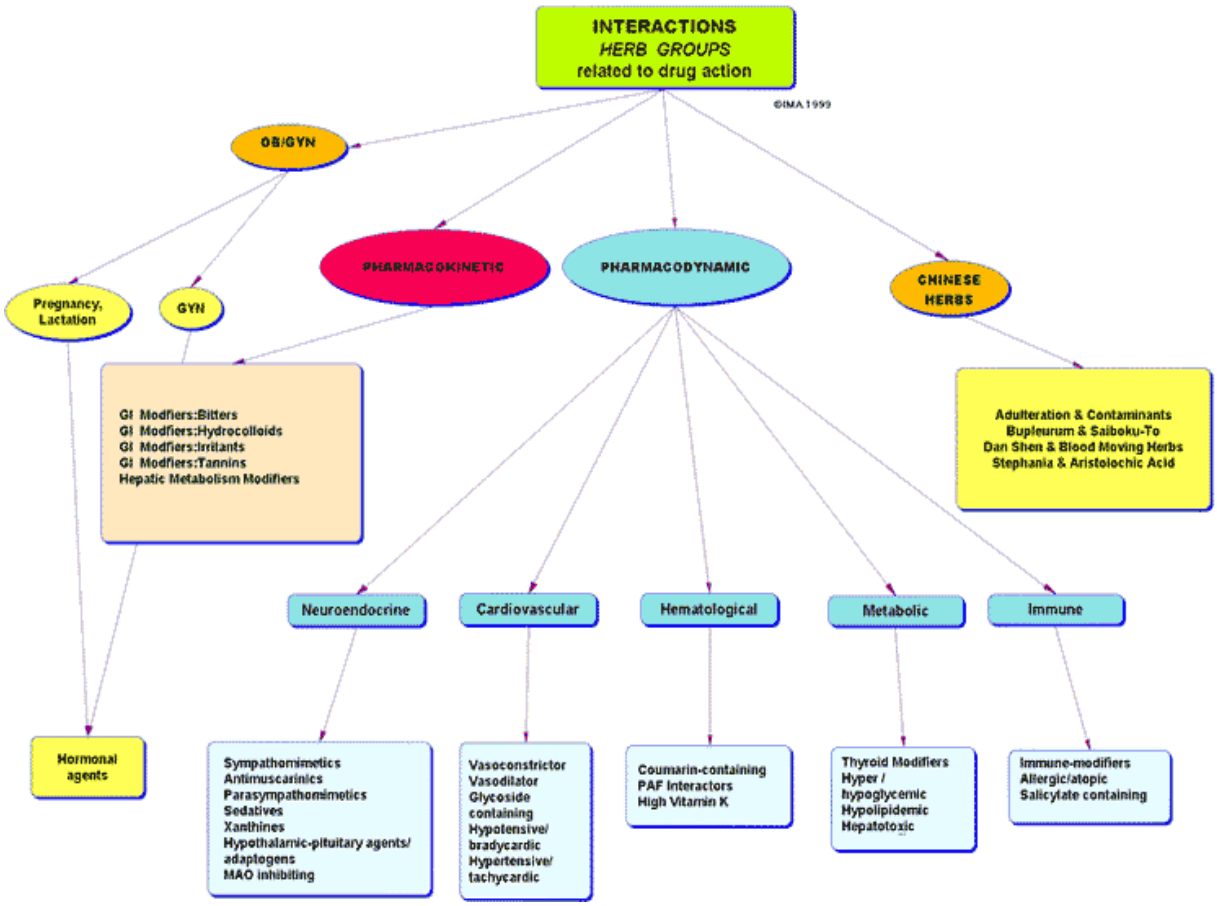
Where the difference between the effective dose and the toxic dose is small. The drug digoxin is an example of this type of drug.

Steep dose response curve; Small changes in the dosage of a drug produce large changes in the drugs concentration in the patients blood plasma.

Saturable hepatic metabolisam; In addition to dose effects the capacity to metabolize the drug is greatly decreased .

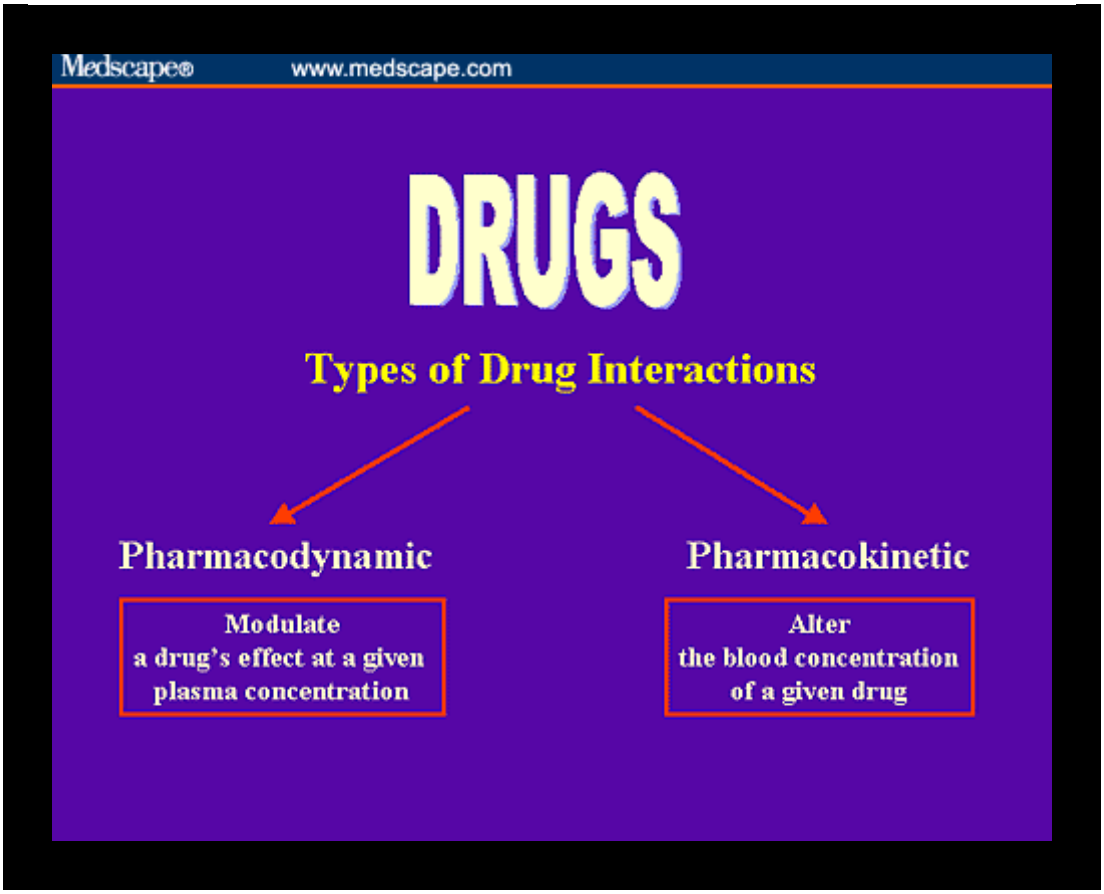
CLASSIFICATION OF DRUG DRUG INTERACTION ;

There are a number of mechanisms by which drugs interact with each other and most of them can be divided into two general categories.


INTERACTIONS
HERB GROUPS
related to drug action
©IMA 1999
OB/GYN
PHARMACOKINETIC
PHARMACODYNAMIC
CHINESE HERBS
Pregnancy, Lactation
GYN
GI Modfiers:Bitters
GI Modfiers:Hydrocolloids
GI Modfiers:Irritants
GI Modfiers:Tannins
Hepatic Metabolism Modifiers
Adulteration & Contaminants
Bupleurum & Saiboku-To
Dan Shen & Blood Moving Herbs
Stephania & Aristolochic Acid
Neuroendocrine
Cardiovascular
Hematological
Metabolic
Immune
Hormonal agents
Sympathomimetics
Antimuscarinics
Parasympathomimetics
Sedatives
Xanthines
Hypothalamic-pituitary agents/ adaptogens
MAO inhibiting
Vasoconstrictor
Vasodilator
Glycoside containing
Hypotensive/ bradycardic
Hypertensive/ tachycardic
Coumarin-containing
PAF Interactors
High Vitamin K
Thyroid Modifiers
Hyper / hypoglycemic
Hypolipidemic
Hepatotoxic
Immune-modifiers
Allergic/atopic
Salicylate containing

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS.

With pharmacokinetic drug interactions, one drug affects the absorption , distribution, metabolisam, or excretion of another. When pharmacodynamic drug interactions occur' two drugs have additive/synergistic or antagonistic pharmacologic effects. Either type of drug interaction can result in adverse effects in some individuals.



PHARMACOKINETIC DRUG DRUG INTERACTIONS

Drug may be interacting at any point during their absorption, distribution ,metabolisam or excretion ,the result may be an increase or decrease in the concentration of either drug at the site of action. As individuals vary in their rate of disposition of any given drug ,the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but it can be vary siginificantly[12].

DRUG ABSORPTION INTERACTION

Most of the drugs are given orally for absorption through the mucous membrane of the GIT, and the majority of interaction that go on within the gut result in reduced rather than the increased absorption[19].

a. Effects of changes in gastro intestinal pH

The passage of drugs through mucous membrane by simple passive diffusion depends upon the extend to which they exist in non ionised lipid soluble form. Absorption is therefore governed by the pka of a drug, its lipid solubilit ,pH of the contents of the gut and various other parameters relating to the pharmaceutical formulation of the drug[19].

Rises in pH due to proton pump inhibitors and H2 receptor antagonists, can markedly reduce the absorption of ketoconazole[19].

b. Adsorption, chelation and other complexing mechanisms

Activated charcoal and antacids can adsorb a large number of drugs.

Eg.Cholestyramine form complexes with digoxin, levothyroxine, warfarin and results in reduced absorption of these drugs.

Antacids reduce the absorption of drugs like ketoconazole, penicillamine, quinolones and tetracyclines by forming less soluble complexes.

c. Effects of changes in gastrointestinal motility

Propantheline delays gastric emptying and reduces paracetamol absorption, where as metoclopramide has the opposite effect. Drugs with anti muscarinic effects decrease the motility of the gut, thus the tricyclic antidepressants can increase the absorption of dicoumarol, probably because the time available for dissolution and absorption but in the case

of levodopa , they may reduce the absorption probably because the exposure time to intestinal mucosal metabolisam is increased[19].

d. Induction or inhibition of drug transporter proteins.

The oral bioavailability of some drugs is limited by the action of drug transporter proteins , which eject drugs that have diffused across the gut lining back into the gut.

Digoxin is a substrate of P-glycoprotein, and drugs that induces this protein, such as rifampicin,may reduce the bioavailability of digoxin[19].

e .Mal- absorption caused by drugs.

Neomycin causes a malabsorption syndrome, similar to that seen with non-tropical sprue. The effect is to impair the absorption of a number of drugs including digoxin and methotrexate[19].

DRUG DISTRIBUTION INTERACTIONS.

Drug distribution to the target site after absorption is determined largely by blood flow to the area and the binding properties of the drug to plasma proteins. Drugs can bind to several blood components , such as albumin, alpha 1-acid glycoprotein, lipoproteins and immunoglobulin. The unbound drug is regarded as the biologically active fraction because it is able to exert its effect on the pharmacological target with in tissues. Therefore, binding to blood components limits the activity of the drug[19].

The mechanism by which drug interactions alter drug distribution include

(1) Competition for plasma protein binding site.

Although competition for plasma protein binding can increase the free concentration of drug after displacement in to plasma, the increase tends to be temporary owing to a compensatory increase in drug disposition.

(2) Displacement of first drug from tissue binding sites.

The importance of displacement of drug from protein binding site has probably been over emphasized, only few drugs are known to cause clinically important interactions by this mechanisms.(e.g. oral anti coagulants, sulfonylureas)

(3) Induction or inhibition of drug transport proteins

It is increasingly being recognised that distribution of drugs into the brain, some other organs such as testes, is limited by the action of drug transporter proteins such as P-glycoprotein . These proteins actively transport drugs out of cells when they have passively diffused in. Drugs that are inhibitors of these transporters could therefore increase the uptake of drug substrates into the brain, which could either increase adverse CNS effects, or be beneficial[41].

DRUG METABOLISAM (biotransformation) INTERACTIONS

Drug metabolisam takes place in the serum, the kidneys, the skin and the intestines, but the greatest proportion is carried out by enzymes that are found in the membranes of the endoplasmic reticulum of the liver cells. The majority of phase 1 oxidation reactions are carried out by cytochrome450.

a) Changes in first pass metabolisam.

i) Changes in blood flow through liver.

A number of highly lipid soluble drugs undergo substantial biotransformation. Drugs first pass through the gut wall and liver and some drugs have a marked effect on the extend of first pass metabolism by altering the blood flow through the liver.

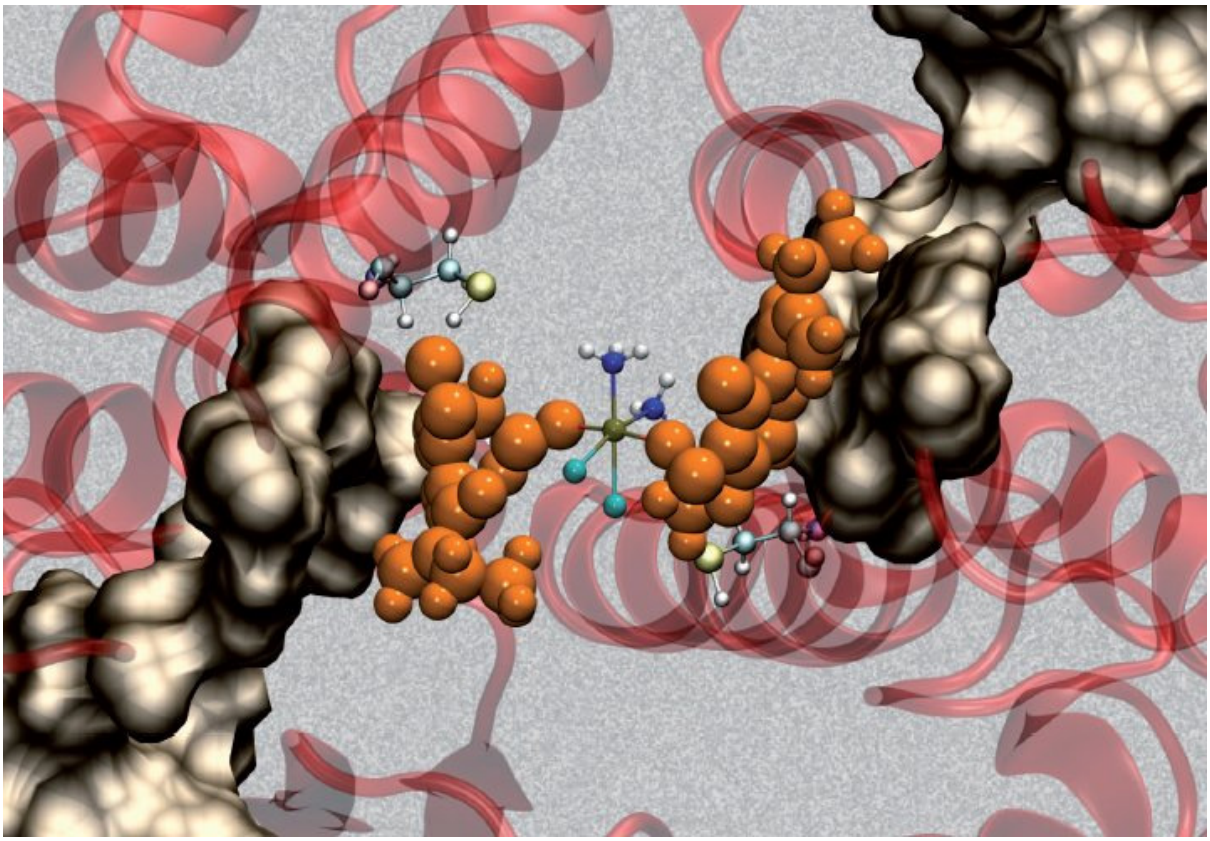
Eg; increase in bioavailability of high extraction beta blockers with hyralazine possibly caused by altered hepatic blood flow, or altered metabolism[19].

ii) inhibition or induction of first pass metabolism;

The gut wall contains metabolising enzymes, principally the cytochrome P450 isoenzymes .Drugs which inhibit or induce this enzyme may increase or decrease the bioavailability of some other drugs[42].

b) Enzyme induction;

Some drugs called “enzyme inducers” are capable of increasing the activity of drug metabolizing enzymes, and increase the metabolism of other drugs and results in reduced drug effect. So, larger doses are needed to maintain the same therapeutic effect. The enzyme induction interactions are delayed in onset and slow to resolve .Examples of enzyme inducers include barbiturates, phenytoin, carbamazepine, griseofulvin, phenytoin, primidone, rifabutin, and rifampin



If drug A is metabolized by cytochrome p450 enzyme and drug B induces or increases the enzymes activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will takes place more rapidly. As a result, enzymatic induction will cause a increase in the drugs effects.

Some drugs, such as ritonavir depending on the situation may act as either an enzyme inhibitor or an enzyme inducer. Drugs metabolized by CYP3A4 or CYP2C9 are particularly susceptible to enzyme induction . In some cases, especially for drugs that undergo extensive first pass metabolism by CYP3A4 in the gut wall and liver, the reduction in serum concentrations of the object drug can be profound.

Enzyme induction resulting in toxic metabolites;

Some drugs are converted to toxic metabolites by drug metabolizing enzymes. For example, the analgesic acetaminophen is converted primarily to non toxic metabolite, but a small amount is converted to a metabolite, but a small amount is converted to a cytotoxic metabolite. Enzyme inducers can increase the formation of the toxic metabolites and increase the risk of hepatotoxicity as well as damage to other organs.

c) Enzyme inhibition;

It is more common than enzyme induction . This results in the reduced metabolism of an affected drug, so that it may begin to accumulate in the body .Enzyme inhibition can occure within 2-3 days, resulting in rapid development of toxicity. The metabolic pathway that is most commonly inhibited is phase 1 oxidation by the cytochrome p450 isoenzyme. Examples of enzyme inhibitors include cimetidine, fluvoxamine, fluoroquinolones (ciprofloxacin, enoxacin)[19].

Enzyme inhibition increasing risk of toxicity;

Most drugs are metabolized to inactive or less active metabolites by enzymes in theliver and intestine. Inhibition of this metabolism can increase the effect of the object drug. If the increase in effect is large enough, drug toxicity may result. This is one of the most common mechanisms by which clinically important drug interactions occur. Since only a few different cytochrome P450 isozyme are involved in drug metabolism and competition between two drugs for these isozymes will occasionally occur. This competition may result in alteration with the metabolism of one or both the drugs.

For example, inhibitors of CYPIA2 can increase the risk of toxicity from clozapine or theophylline. Inhibitors of CYPZC9 can increase the risk of toxicity from phenytoin, tolbutamide, and oral anticoagulants such as warfarin. Inhibitors of CYP3A4 can increase the risk of toxicity from many drugs including carbamazepine, cisapride, cyclosporine, ergot alkaloids, lovastatin, pimozide, protease inhibitors, rifabutin, simvastatin, tacrolimus and vinca alkaloids.

Enzyme inhibitors resulting in reduced drug effect:

A small number of drugs are not active in the form administered to patients. These drugs are known as prodrugs and require activation by enzymes in the body before they can produce their effect. Inhibition of the metabolism of these prodrugs may reduce the amount of active drug formed, and decrease or eliminate the therapeutic effect. For example, the analgesic and toxic effects of codeine appeared to result from its conversion to morphine by

CYPZD6. Thus CYPZD6 inhibitors can impair the therapeutic effect of codeine. CYPZD6 inhibitors may similarly effect the analgesic effect of hydrocodone.

d) Genetic factors in drug metabolism;

Depending on the genetic polymorphism of cytochrome P450 isoenzymes, individuals have varying ability to metabolize certain drugs.

Individuals fall in 'poor or slow metabolisers' or 'fast or extensive metabolisers'[19].

e) Cytochrome P450 isoenzymes and predicting drug interaction;.

By doing invitro tests with human liver enzymes, it is often possible to explain why and how some drugs interact.

DRUG ELIMINATION/EXCRETION INTERACTIONS;

With the exception of the inhalational anaesthetics, most drugs are excreted either in the bile or in the urine. Interference by drugs with renal tubular fluid pH, with active transport systems and with blood flow to the kidneys can alter the excretion of other drugs[19].

a) Changes in urinary pH;

Passive reabsorption of drugs depends upon the extend to which the drugs exists in the non ionised lipid soluble form, which in turn depends on its pKa of the urine. Thus at high pH values (alkaline),weakly acidic drugs (pKa 3 to 7.5) largely exist as ionized lipid insoluble molecules, which are unable to diffuse into the tuble cells and will therefore remain in the urine and be removed from the body. The converse will be true for weak bases with pKa values of 7.5 to 10.5. Thus, pH changes that increase the amount in the ionized form (alkaline urine for acidic drugs, acid urine for basic drugs) increase the loss of drug, where as moving the pH in the opposite direction will increase their retention.

For example, probenecid can increase the serum levels of cephalosporins, dapsone, methotrxate, penicillins, quinolones. Salicylates and some other NSAIDs can increase serum level of methotrexate resulting in the possibility of serious toxicity.

b) Changes in active renal tubular excretion;

Drugs that use the same active transport systems in the renal tubules can compete with one another for excretion. Eg; probenecid reduces the excretion of penicillin and other drugs[19].

c) Changes in urinary blood flow;

The flow of blood through the kidney is partially controlled by the production of renal vasodialatory prostaglandins. If the synthesis of these prostaglandins is inhibited,the renal excretion of some drugs may be reduced. Eg; Increase in serum lithium seen with some NSAIDs[19].

d) Biliary excretion and entero- hepatic shunt;

i) **Enterohepatic recirculation**;

A number of drugs are excreted in the bile, either unchanged or conjugated (Eg; as the glucuronide) to make them more water soluble. Some of the conjugates are metabolized to the parent compound by the gut flora and are then reabsorbed. This recycling process prolongs the stay of the drug within the body, but if the gut flora are diminished by the presence of an anti- bacterial , the drug is not recycled and is lost more quickly. Eg; The failure of oral contraceptives with concurrent use of penicillins or tetracyclines[41].

ii) Drug transporters;

Numerous drug transporter proteins (both from the ABC family and SLC family) are involved in the hepatic excretion and secretion of drugs into the bile. The bile salt export pump (ABCB 11) is known to be inhibited by a variety of drugs including ciclosporins, glibenclamide and bosentan. Inhibition of this pump may increase the risk of cholestasis.

ABCB1 has a role in the renal elimination of substances by active secretion into the urine. It is localized at the brush- border membrane of the proximal renal tubule (luminal side), where it pumps drug molecules into the tubular filtrate. ABCB1 inhibition results in an increase in the systemic exposure and tissue distribution of drugs that are ABCB1 substrates, whereas the induction of ABCB1 leads to a decrease in systemic exposure. ABCB1 that is

expressed in the liver also has a role in the elimination of unchanged drugs and metabolites. Localized in the canalicular membrane of hepatocytes, the efflux protein pumps drug molecules into the bile, where they can be reabsorbed from the intestine or eliminated in the faeces.

The directional movement of drugs across organs such as the gastrointestinal tract, liver and kidneys requires drug uptake transporters as well as efflux transporters. For example, organic anion transporters (OATs) and organic anion- transporting polypeptides (OATPs) are expressed in organg of importance to drug disposition can mediate and response, such as the CNS, liver and intestine, and can mediate the cellular uptake of several structurally diverse compounds. Typically, larger and more lipophilic organic anions are transported in the liver by OATPs, whereas small hydrophilic organic anions are extracted by OATs, which are highly expressed on the basolateral side of renal proximal tubules.

e) Changes in renal secretion;

For some drugs , active secretion into the renal tubules is an important route of elimination. For example, digoxin is eliminated primarily through renal excretion, and drugs such as amiodarone, clarithromycin, itraconazole, propafenone, and quinidine can inhibit this process leading to digoxin toxicity may result when administered concomitantly[40].

PHARMACODYNAMIC DRUG INTERACTIONS;

Pharmacodynamic interactions can be categorized broadly as synergistic (when the effect of two drugs is greater than the sum of their individual effects); antagonistic (drugs with opposing pharmacologic effects); additive (when the effect of two drugs is merely the sum of the effects of each); and sequence –dependent(when the order in which two drugs are given governs their effects.

The two drugs may or may not act on the same receptors to produce such effects[10].

1. Additive or synergistic interactions;

When two or more drugs with similar pharmacodynamic effects are given, the additive effects may result in excessive response and toxicity. Examples include combinations of drugs that prolong the QT interval resulting in ventricular arrhythmias, and combining drugs with hyperkalemic effects resulting in hyperkalemia. Eg . Many diuretics lower plasma K+ concentration and there by enchances toxic actions of cardiac glycosides

(digitalis) and predispose to glycoside toxicity with antiarrhytmic drugs that prolong cardiac action potential and Monoamine oxidase inhibitors increase the amount of noradrenaline stored in noradrenergic nerve terminals and there by interact dangerously with drugs, such as " Ephedrine or tyramine", that work by releasing stored nor adrenaline[41].

2. Antagonistic or opposing interactions;

Drugs with opposing pharmacodynamic effects may reduce the response of one or both drugs. For example, NSAIDs oppose the antihypertensive effect of ACE inhibitors or loop diuretics; glucocorticoids oppose the blood glucose lowering effect of antidiabetics; megestrol oppose the antineoplastic effect of antineoplastics; vitamin K oppose the anticoagulant effect of anticoagulants[19].

3 Drug or neurotransmitter uptake interaction;

A number of drugs with actions that occur at adrenergic neurons can be prevented from reaching those sites of action by the presence of other drugs. The tricylic antidepressants prevent the re uptake of noradrenaline into peripheral adrenergic neurons. Thus, patients taking tricyclines and given parenteral noradrenaline have a markedly increased response (hypertension, tachycardia)[19].

PHARMACEUTICAL INTERACTIONS;

Pharmaceutical interactions occur when two compounds interact because of they are incompatible either physically or chemically.

Although dramatic advances have been made in the study of drug drug interaction mechanisms over the past few decades, there is still much to learn about these. Thus, many of the mechanism concepts useful today will be refined in the future, yielding a picture closer to the truth, it also should be kept in mind that for some drug drug interactions there may be more than one mechanism occurring simultaneously.

In case of reversible inhibition the enzyme inhibited by the first drug may not be recognised by the concomitantly administered drug which is the substrates of the inhibited enzyme and it may take few days for recovery. Eg; cemetidine and macrolide antimicrobials directly form complex with heme moiety of CYP isoenzymes. Where as irreversible inhibition leads to inactivation of the enzyme system,also known as mechanism based or

suicide inhibition. Eg.Ethinyiestradiol, gestodene and levonorgesterol are reported to cause mechanism based inhibition[42]

It has long been established that elderly patients use more medicines than younger age groups and thus have a greater risk of experiencing a drug drug interaction. In elderly patients, the reserve capacity of many organs may be considerably reduced, and because of this erosion, there is narrowing of the safety margin between the therapeutic and toxic dose of drugs.

Pharmacokinetics effects of drugs may be increased or decreased in the elderly patient. Age related differences in kinetics in elderly is primarily due to diminished renal function, altered proportion of body fat and water , reduced cardiac output and some degree of altered hepatic metabolism.

Pharmacodynamic interactions are also influenced by age. The elderly show an increased response to ACE inhibitors, they show an increased responsiveness to propanolol. The inotropic effect of Theophylline is increased with age, but its bronchodilator effect is reduced. The anticoagulant effect of warfarin is increased in elderly patients due to greater fragility of the hepatic synthesis of clotting factors.

Phenothiazine, diuretics, antihypertensives, beta adrenoreceptor antagonists, antidepressants, NSAIDs, benzodiazepines and lignocaine are all examples of drugs that are likely to produce enhanced pharmacological or toxic effects in the elderly

Drug drug interactions can have potentially life-threatening consequences in older adults,who often take several drugs at once for multiple diseases. Elderly patients are more susceptible to drug interactions than younger patients because of age-related physiologic changes and the sheer number of drugs they are taking

LITERATURE REVIEW

Fita*Rahmavati&etal.*(2007)Conducted a study in a private hospital at Yogyakarta in Indonesia from july until December 2007. The finding of this study showed that the mean number of medication per cases per day was 5.8 + 2.1 (+SD) Of the 100 cases ,65%cases had experienced potential DDIs range from 1to 17 . Of total 204 DDIs incidences, 25% were of significance level 1 and 39% of significance level 2. Twelve cases (12%) have more than 4 incidences of DDIs. Our study showed that the number of potential DDIs increased as the number of medications used per day increased. Geriatric patients taking nine or more medication tended to have more DDIs (6.8+5.5) in comparison to those with one to two medications with no DDIs. The result of liner regression analysis indicated that number of medication used per day have positive relationship on number of DDIs (p =0.000). Incidence of DDIs in geriatric patients was frequent and pharmacist can play a critical role in managing medication therapy of patients with collaboration with other professional health care to prevent adverse drug reactions [38].

***Mr.Hemendragautam* (2006)**in may did a study on drug drug interactions, in Medicine Department, K.L.E.S Hospital and medical Research center, Belgaum, Karnataka. In 85 patients 207 potential drug drug interactions were found out in his study. In his study, the most common drug classes involved in DDIs were anti hypertensives and antibiotics . There was a uniform increase in the percentage of DDIs with an associated increase in the number of drugs.[20]

***Daniel C.Malone et al* (2005)** suggested the prevalence of 25 clinically important potential drug drug interactions DDIs in a population represented by the drug claims databases of a pharmacy benefit management company PBM was studied . The number of DDIs ranged from 37 for pimozide and azole anti fungal to 127,684 for warfarin and a non steroidalanti inflammatory drugs. The highest prevalence and highest case exposure rate occurred with the warfarin NSAID combination. The combination with the lowest overall prevalence differs from the combination with the lowest case- exposure rate. Number of cases, prevalence, and case exposure rates for both sexes generally increased with age. An estimated 374,000 participants were exposed to a clinically important DDI during a 25 month period. Between 20% and 46% of prescription drug claims were reversed for a medication with a drug interaction when a warning about the interaction was sent to the pharmacy.[21]

Robert A.Hamilton& et al, studied Frequency of Hospitalization after Exposure to known drug drug interactions in a Medicaid population. A matched pair case control analysis of Medicaid claims was performed to determine the risk of hospitalization associated with drug drug interactions. Patients were hospitalized and controls were not. They were randomly matched based on contemporaneous eligibility for Medicaid benefits. Odds ratios for hospitalization in patients exposed to one of the interacting agents. When confidence intervals did not overlap, the odds ratio was considered to be significantly increased. Odds ratios were significantly increased for many interacting drug pairs; and were associated with commonly recognized interactions achieved significance only with theophylline . In the Medicaid population, exposure to a number of drug drug interactions was associated with a significantly increased risk of hospitalization.[22]

L. Bjermm, J. Sogaard, J. Halls, analyzed the occurrence of multiple drug use (poly pharmacy, pp) in the population and the identify individuals particularly prone to PP.On a random day, 8.3% of the populations were exposed to minor PP and 1.2% to major PP. The prevalence of PP increased with age, and from the age of 70 years, two thirds of all drug users were PP users. Drug use was 50% more prevalent among women than men, but over the age of 70, the sexes did not differ in the prevalence of major PP. Many different drug combinations were found, and among major PP users (n = 5443), two thirds had their own unique regimen, different from all other drug users. Cardiovascular drugs and analgesics were often involved in PP among the elderly, while asthma drugs, psychotropic drugs and anti ulcer drugs were predominant among individuals exposed to PP. The odds ratio (OR) for major PP was substantially increased for individuals treated for cardiovascular diseases(OR, 4.5), anaemia (OR ,4.1) and respiratory diseases (OR, 3.6) . Document the degree of polypharmacy, the frequency diseases of adverse drug related events (ADEs) leading to emergency physicians, and the frequency of potential adverse drug interactions (PADIs) in medication regiments of elderly patients in the ED.[23]

Franklin E. May ,& et al **(2004)** studied effect of multiple drug administration on drug reactions in 10,518 patients hospitalizes on a general medical service during a five year period. Drug groups, including analgesic, antacid, anti arrhythmic, antimicrobial, anticoagulants, antihypertensive, anti inflammatory, diuretic, and sedative tranquilizer drugs, were selected for study. The average number of adverse drug reactions for the anticoagulant and anti hypertensive drug groups was higher(p 0.05) than for all other drugs groups when

classified by the number of drugs being taken concurrently (i.e, 0 to 5,6 t0 10, etc). The rate of reaction for anticoagulant and antihypertensive drug groups was higher (p 0.001)than the rate for other drug groups studied. These data suggest a higher risk of adverse drug reactions for patients receiving multiple drugs. The increased risk may result from drug interactions.[25]

***Donna M. Fick, RN; &et al* (2003)** Conducted a study for updating the Beers criteria for potentially Inappropriate Medication use in Older Adults. This study identified 48 individual medications or classes of medications to avoid in older adults and their potential concerns and 20 diseases/ conditions and medications. Of these potentially inappropriate drugs, 66 were considered by the panel to have adverse outcomes of high severity.[26]

***David N. Juurlink& et al* (2003)** determined whether elderly patients admitted to hospital with specific drug toxicities were likely to have been prescribed an interacting drug in the week prior to admission. During the 7 year study period, 909 elderly patients receiving glyburide were admitted with a diagnosis of hypoglycaemia. In the primary analysis , those patients admitted for hypoglycaemia were more than 6 times as likely to have been treated with co trimoxazole in the previous week adjusted odds ratio , 6.6;95 confidence interval, 4.5 – 9.7. Patients admitted with digoxin toxicity n;1051 were about 12 times more likely to have been treated with clarithyromycin adjusted odds ratio, 11.7; 95% confidence interval, 7,5 – 18.2 in the previous week, and patients treated with ACE inhitors admitted with a diagnosis of hyperkalemia n; 523 were about 20 times more likely to have been treated with a potassium sparing diuretic adjusted odds ratio, 20.3; 95% confidence interval, 13.4- 30.7 in the previous week. No increased risk of drug toxicity was found for drugs with similar indications but no known interactions amoxicillin, cefuroxime, and indapamide , respectively, prescription of contraindicated and interacting drugs in elderly patients admitted in hospital. Another study determines the prevalence and predictors of inappropriate drug prescribing defined by expert national consensus panel drug utilization review criteria for community dwelling older people.[27]

***Kenneth E. Schmader& et al* (2004)**drtermined if inpatient or outpatient geriatric evaluation and management, as compared with usual care, reduces adverse drug reactions and sub optimal prescribing in frail elderly patients. For serious adverse drug reactions, there were no inpatient geriatric unit effects during the inpatient or outpatient follow up periods. Outpatient geriatric clinic care resulted in a 35% reduction in the of a serious adverse drug reaction compared with usual care (adjusted relative risk =0.65; 95% confidence interval ; 0.45 to 0.93). Inpatient geriatric unit care reduced unnecessary and inappropriate drug use

and under use significantly during the inpatient period (p o0.05). Outpatient geriatric clinic care reduced the number of conditions with omitted drugs significantly during the outpatient period (p 0.05) .Another study estimates the incidence of serious and fatal adverse drug reactions(ADR) in hospital patients.[29]

Mark H. Beers, & et al determined how often emergency department physicians prescribe medications that can adversely interact with other medications that their patients are already taking, which patients are at hihhest risk for potential adverse reactions, and which medications most frequently lead to adverse interactions. In this study evaluated 424 randomly selected visits to a hospital emergency department made by 186 persons over age 65 and 238 younger adults; all of the subjects were discharged without hospital admission. Forty seven percent of visits led to added medication, and in 10% of the visits in which at least one medication was added, a new medication added a potential adverse interaction. The interactions were dererminded by a computer program, were reviewed using explicit criteria, and were excluded if of uncertain or trivial clinical significance, rare, or not established at presentation was the best predictor of whether a potential interaction would be introduced.[30]

***VerenaBergk, et al,(*2004)** Estimated the risk associated with drug interaction in a larger population when not only the severity of possible clinical events but also measures of their prevention(manageability, modulating factors are considered. More then 52%of the patients received combination therapy. Interaction information was available in a standard sorce(DRYGDEX; Thomas MICROMEDEX, Greenwood Village, Colo) for only 1029 of all 13,672 individual prescribed drug pairs. Of the dwg pairs, 881 (6.45%) were identified as interacting. Of these 881 interactions, 132(15%) were of major severity but 101 of 132 (76.5%) were considered manageable . Only 31(23.5%) of 132 major interactions (ie, 31/881[3.5% of all interacting pairs]) offered on management options and should thus be avoided.[31]

Jerry H. & et al assessed the incidence and preventability of adverse drug events among older persons in the ambulatory clinical setting. There were 1523 identified adverse drug events, of which 27.6%(421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person - years, Of the adverse drug events, 578(38.0%) were categorized as serious,life threating, or fatal; 244 (42.2%) of these more severe events

were deemed preventable compared with 277 (18.2%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n= 89,21.1%) also were common. Cardiovascular medications (22.4%), followed by diuretics (22.1%), non opiod analgesics (15.4%), hypoglycaemic (10.9%), and anticoagulants (10.02%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6%), gastrointestinal tract (21.1%), hemorrhagic (15.9%), metabolic/ endocrine (13.8%) and neuropsychiatry (8.6%) events were the most common types of preventable adverse drug events.[32]

David W. Bates & et al* (1995*) assessed incidence and preventability of adverse drug events (ADEs) and potential ADEs. To analyze preventable events to potential ADEs were identified. Extrapolated event rates were 6.5 ADEs and 5.5 potential ADEs per 100 non obstetrical admissions, for mean numbers per hospital per year of approximately 1900 ADEs and 1600 potential ADEs. Of all ADEs, 1% was fatal (none preventable), 12% life threatening, 30% serious, and 57% significant. Twenty eight percent were judged preventable. Of the life threatening and serious ADEs, 42% were preventable, compared with 18% of significant ADEs. Error resulting in preventable ADEs occurred most often at the stages of ordering (56%) and administration (34%); transcription (6%) and dispensing error (4%) were less common. Error were much more likely to be intercepted if the error occurred earlier in the process; 48% at the ordering stage vs. 0% at the administration stage.[33]

Richard Harrison & et al from old age psychiatry, Castleside offices, Care of the Health of the Elderly, Newcastle General Hospital, Westgate Road, Newcastle conducted a cross sectional survey of patient drug prescriptions on two elderly psychiatric wards was carried out to estimate the potential of drug drug interactions. Two standardised databases, British National Formulary (BNF; British Medical Association & Royal pharmaceutical society of Great Britain, 2007) and upto data (www. Uptodate.com), were employed. A majority (96%) of drug prescriptions in their study could potentially cause drug drug interactions. Most patients were on multiple drugs (on average eight drugs per patient). There was poor concordance between the two databases; BNF picked up fewer cases of potential drug drug interactions than upto date (43 v152 instances) and they also estimated the potential for hazardousness differently.

MaysaaMahmood, Daniel C.Malone& et al did a retrospective, cross sectional database analysis of pharmacy records to assess the prevalence of 25 clinically important

(DDIs) in the ambulatory care clinics of the Department of Veterans Affairs medical centers (VAMCs). The 25 DDIs were categorized into four main categories on the basis of the therapeutic classification of the medications involved in the drug pairs. The study population included 2,795,345 patients who filled prescriptions for medications involved in potential DDIs across 128 VAMCs. The highest DDI exposure rate was 129.2 per 1,000 recipients of monoamine oxidase inhibitors (MAOIs) that occurred with combinations of selective serotonin reuptake inhibitors (SSRIs). The lowest DDI exposure rate was 0.01 per 1,000 warfarin recipients who had the warfarin and sulfinpyrazone combination. The analysis of pharmacy records of veterans who filled prescriptions at the outpatient settings within VAMC found an overall rate of 2.15% for potential DDIs. Case exposure rates were greatest for veterans receiving SSRIs and MAOIs, ganciclovir and zidovudine, anticoagulants and thyroid hormones, and warfarin and nonsteroidal anti-inflammatory drugs.[35]

Daniel C. Malone, David S.Hutchins& et al. Conducted a retrospective cross sectional analysis of pharmaceutical claims for almost 46 million participants in a PBM to determine the frequency of 25 DDIs previously identified as clinically important. A DDI was counted when drugs in potentially interacting combinations were dispensed within 30 days of each other during a 25 month period between April 2000 and June 2002. The number of DDIs ranged from 37 for pimozide and an azole antifungal to 127,684 for warfarin and a nonsteroidal anti-inflammatory drug (NSAID). The highest prevalence (278.56 per 100,000 persons) and highest case exposure rate (242.7 per 1,000 warfarin recipients) occurred with the warfarin - NSAID combination. The combination with the lowest overall prevalence (cyclosporine and a rifamycin, 0.10/100,000) differed from the combination with the lowest case exposure rate (pimozide and an azole antifungal recipients). Number of cases, prevalence, and case exposure rates for both sexes generally increased with age. An estimated 374,000 plan participants were exposed to a clinically important DDI during a 25 month period. Between 20% and 46% of prescription drug claims were reversed (cancelled) for a medication with a drug interaction when a warning about the interaction was sent to the pharmacy. Analysis of prescription claims data from a major PBM found that 374'000 of 46 million plan participants had been exposed to a potential DDI of clinical importance.[36]

IK Bjorkman, J Fastbom, IK Schmidt, and CB Bernsten conducted study to detect the frequency of potential drug drug interactions (DDIs) in an outpatient group of elderly people in 6 Europen countries, as well as to describe differences among countries. Drug use data were collected from 1601 elderly persons living in 6 European countries. The study

population participated in a controlled intervention study over 18 months investigating the impact of pharmaceutical care. Potential DDIs were studied using a computerized detection program. Results found that the elderly population used on average 7.0 drugs per person ; 46% had at least 1 drug combination possibly leading to a DDI. On average, there were 0.83 potential DDIs per person . Almost 10% of the potential DDIs were classified to be avoided according to the Swedish interaction classification system, but nearly one third of them were to be avoided only for predisposed patients. The risk of subtherapeutic effect as a result of a potential DDI was as common as the risk of adverse reactions. Furthermore, they found differences in the frequency and type of potential DDIs among the countries.[37]

***Prof. Dr.Joice Mara Cruciol Souza &et al,* (2006)** from Brazil conducted a study in 11500 patients for 4 month period and the overall frequency of potential DDI was found to be 49.7%. The frequency of the potentially major DDI was 3.4%. The rate of DDI was significantly associated to in patient's gender, sex and number of drugs.

Rachel P. Riechelmann. et al., has conducted a study on " potential Drug Interactions and Duplicate Prescriptions Among Cancer patients" in princess Margaret Hospital, Toronto, in 2006. In this study 276 potential drug interactions were identified in 109 patients. The majority of drug interactions were of moderate severity (77%), and 49% of them were supported by levels 1 or 2 scientific evidence. The drug interaction Facts software, version 4.0, was used to identify potential drug interactions and to classify them by level of severity (major, moderate, or minor) and the strength of scientific evidence for them (using categories [1-5] of decreasing certainity).

J. Kragstrup a nalyzed, The prevalence of PP increased with age, and from the age of 70 years, two thirds of all drug users were PP users. Drug use was 50% more prevalent among women than men, but over the age of 70, the sexes did not differ in the prevalence of major PP. Many different drug combinations were found, and among major PP users (n = 5443), two thirds had their own unique regimen, different from all other drug users. Cardiovascular drugs and analgesics were often involved in PP among the elderly , while asthma drugs, psychotropic drugs and anti ulcer drugs were predominant among individuals exposed to PP. The odds ratio (OR) for major PP was substantially increased for individuals treated for cardiovascular diseases(OR, 4.5), anaemia (OR ,4.1) and respiratory diseases (OR, 3.6) . Document the degree of polypharmacy, the frequency diseases of adverse drug related

events (ADEs) leading to emergency physicians, and the frequency of potential adverse drug interactions (PADIs) in medication regiments of elderly patients in the ED.[23]

Susan M Wallestdt et al.**(2006)**(Inclusion critera in this register-based study were inhabitants in Region Västra Götaland, Sweden, who, at ≥65 years of age and between 1st July 2006 and 30th June 2010, filled their first MDD prescription. For each individual, prescribed drugs were estimated at three month intervals before and after (maximum 3 years, respectively) the first date of filling an MDD prescription (index date)

A total of 30,922 individuals matched the inclusion criteria (mean age: 83.2 years; 59.9% female). There was a temporal association between the transition to MDD and an increased number of drugs: 5.4±3.9 and 7.5±3.8 unique drugs three months before and after the index date, respectively, as well as worse outcomes on several indicators of prescribing quality. When either data before or after the index date were used, a multi-level regression analysis predicted the number of drugs at the index date at 5.76 (95% confidence limits: 5.71; 5.80) and 7.15 (7.10; 7.19), respectively, for an average female individual (83.2 years, 10.8 unique diagnoses, 2.4 healthcare contacts/three months). The predicted change in the number of drugs, from three months before the index date to the index date, was greater when data before this date was used as compared with data after this date: 0.12 (0.09; 0.14) versus 0.02 (−0.01; 0.05).

After the patients entered the MDD system, they had an increased number of drugs, more often potentially harmful drug treatment, and fewer changes in drug treatment. These findings support a causal relationship between such a system and safety concerns as regards prescribing practices.

CB Bernsten **2002:** To detect the frequency of potential drug-drug interactions (DDIs) in an outpatient group of elderly people in 6 European countries, as well as to describe differences among countries. DATA SOURCES AND METHODS: Drug use data were collected from 1601 elderly persons living in 6 European countries. The study population participated in a controlled intervention study over 18 months investigating the impact of pharmaceutical care. Potential DDIs were studied using a computerized detection program. RESULTS: The elderly population used on average 7.0 drugs per person; 46% had at least 1 drug combination possibly leading to a DDI. On average, there were 0.83 potential DDIs per person. Almost 10% of the potential DDIs were classified to be avoided according to the Swedish interaction classification system, but nearly one-third of them were to be avoided

only for predisposed patients. The risk of subtherapeutic effect as a result of a potential DDI was as common as the risk of adverse reactions. Furthermore, we found differences in the frequency and type of potential DDIs among the countries. CONCLUSIONS: Potential DDIs are common in elderly people using many drugs and are part of a normal drug regimen. Some combinations are likely to have negative effects; more attention must be focused on detecting and monitoring patients using such combinations. As differences in potential DDIs among countries were found, the reasons for this variability need to

***Paul smith,* 2005** studied Computerised drug interaction surveillance systems (CIS) may be helpful in detecting clinically significant drug interactions. Experience with CIS reveals that they often yield alerts with questionable clinical significance, fail to provide relevant information on risk factors for the adverse reaction of the interaction and fail to detect all significant drug interactions. These problems highlight the importance of transparency and selectivity in choosing the drug interactions to be included in CIS. In The Netherlands, the Working Group on Pharmacotherapy and Drug Information is responsible for maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

Methods:

The Working Group developed an evidence-based procedure for structured assessment of drug-drug interactions and revised all drug interactions in the CIS accordingly.

Results:

For every drug interaction four core parameters were assessed: (i) evidence on the interaction; (ii) clinical relevance of the potential adverse reaction resulting from the interaction; (iii) risk factors identifying patient, medication or disease characteristics for which the interaction is of special importance; and (iv) the incidence of the adverse reaction. On the basis of this assessment the drug-drug interactions for inclusion in the CIS were selected. After revision of the drug combinations in the KNMP-CIS, the Working Group

judged 22% of the combinations to be not interacting and another 12% to be interacting but not requiring action.

On the basis of this assessment the subset of drug combinations for which interaction alerts are generated and the information on management of a drug interaction alert for users of the CIS were adapted. When an alert is generated by the CIS, the user of the system is supplied with comprehensive information on the four core parameters, the mechanism of the interaction and critical information for management of the interaction for the individual patient.

J.Sogaard, studied Polypharmacy, the simultaneous use of multiple drugs, is associated with adverse drug reactions, medication errors, and increased risk of hospitalization. When the number of concurrently used drugs totals five or more (major polypharmacy), a significant risk may be present. AIM: To analyse the interpractice variation in the prevalence of major polypharmacy among listed patients, and to identify possible predictors of major polypharmacy related to the practice.[23]

Methods:

Prescription data were retrieved from the Odense Pharmacoepidemiological Database, and individuals subject to major polypharmacy were identified. The age and sex-standardized prevalence rate of major polypharmacy was calculated for each practice in the County of Funen in Denmark (n = 173), using the distribution of age and sex of the background population as a reference. The practice characteristics were retrieved from the Regional Health Insurance System. Possible predictors of major polypharmacy related to the general practitioners (GPs) were analysed using backward stepwise linear multiple regression.

Results:

A six-fold variation between the practices in the prevalence of major polypharmacy was found (16 to 96 per 1000 listed patients; median = 42). Predictors related to the practice structure, workload, clinical work profile, and prescribing profile could explain 56% of the variation. CONCLUSION: A substantial part of the variation in major polypharmacy between practices can be explained by predictors related to practice[23].

AIM AND OBJECTIVES

AIM:

- The aim of the present study was to Identification of drug drug interaction and modification of prescriptions in hospitalized geriatric patients in a tertiary care teaching hospital.

OBJECTIVES:

- To identification of drug drug interaction of prescriptions in hospitalized geriatric patients.
- To modify the prescriptions indicating the drug drug interactions in hospitalized geriatric patients in a tertiary care hospital.
- To determine the drug drug interaction and the association between the number of drugs used per day per patient during hospitalized.

PLAN OF THE WORK

The present dissertation work was planned to conduct a Identification of drug drug interaction and modification of prescription in hospitalized geriatric patients in a tertiary care teaching hospital. The dissertation work was planned to be conducted in Gejo hospital, kottayam,(dist), kerala.

The plan of work includes:

- Submission of the protocol for getting the approval from Ethical committee.
- To get oral consent from patients
- To design a data collection form.
- Collection of case histories of the patients with cutaneous DDIs.
- Evaluvation of collected data.
- Drug drug interactions determined by using Multidrug interaction checker- Medscape.
- Data analysis with the help of computer using Microsoft Excel 2007.

METHODOLOGY

STUDY DESIGN :

This study is prospective observational study. Identification of drug- drug interaction and modification of prescriptions in hospitalized geriatric patients in a tertiary care teaching hospital.

STUDY SETTING:

This study was conducted in Gejo hospital, kottayam (dist), kerala.

STUDY POPULATION :

A minimum of 100 patients admitted in the medicine wards were taken for the study.

DURATION OF STUDY:s

The study was carried out for a period of 6 months.

STUDY CRITERIA :

INCLUSION CRITERIA:

1. Patients of age 65 year and above.
2. Patients hospitalized for two days and more.

EXCLUSION CRITERIA :

1. Patients below the age of 65 years.
2. Patients admitted to hospital before the commencement of the study.

STUDY VARIABLES :

1. Age
2. Gender
3. Current medical history(diagnosis)
4. Medicines prescribed

STUDY PROCEDURE :

Research type was observational prospective. The datas were collected from 105 cases of hospitalized geriatric patients. The datas were collected from patients satisfying inclusion criteria.

The variables analyzed were general characteristics of the patient (gender, age), current medical history (diagnosis), and medicines prescribed during hospitalization. The medication use of geriatric patients during hospitalization were recorded. Then, the medications were classified according to pharmacological classification. To look for potential drug drug interactions (DDIs) every combination of prescribed drugs were analyzed by using the Multidrug interaction checker – Medscape. DDIs is defined as a modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either drug.

The particular interaction may be the result of a chemical – physical incompatibility of the two drugs or a change in the rate of absorption or the quality absorbed in the body, the binding ability of either drug, or an alteration in the ability of receptor sites and cell membranes to bind either drug. Most adverse drug-drug interactions are either pharmacodynamic or pharmacokinetic in nature. Depending on the severity of interaction, DDIs are classified as major (an adverse effect can cause permanent damage or life risk), Moderate (an adverse effect can harm and treatment is required), Minor (small or no clinical effect, with no treatment required). The matching results of DDIs is classified into five categories (significance level 1 to 5). In this classification , drug interactions are at significance level 1 when interaction categories are divided into potentially severe or life threatening interaction; occurrence has been suspected, established or probable in well controlled studies; contraindicated drug combinations also comes under this group. Interaction at significance level 2 can cause deterioration in a patient's clinical status; occurrence has been suspected, established or probable in well controlled studies.

A potential drug drug interaction at significance level 3 presents a potential for minor effects; occurrence has been suspected, established or probable in well controlled studies. While drug drug interaction at significance level4 might cause moderate-to-major effects; but data is very limited. Then, drug interaction at significance level 5 may cause minor to major effects; occurrence is unlikely or there is no good evidence of an altered clinical effect.

OBSERVATIONS AND RESULTS

TABLE 1: AGE DISTRIBUTION OF GERIATRIC PATIENTS

Age group	No. of cases	Percentage
65-69	49	46.66
70-74	32	30.47
75-79	8	7.62
80-85	16	15.23
	Total=105	100%

Of the total of 105 patients enrolled for the study, 49 patients were there in the age group of 65-69 yrs (46.66%), 32 patients came under the age group of 70-74 yrs (30.47%), 8 patients came under the age group of 75-79yrs(7.62%) and 16 patients came in 80-85 yrs age group (15.23%).

It was also found that:

The average age of the total population was 73.65±5.77 yrs.

The average age of the male population was 74.16± 5.86yrs.

The average age of the female population was 72.93±5.60yrs.

AGE DISTRIBUTION OF GERIATRIC PATIENTS

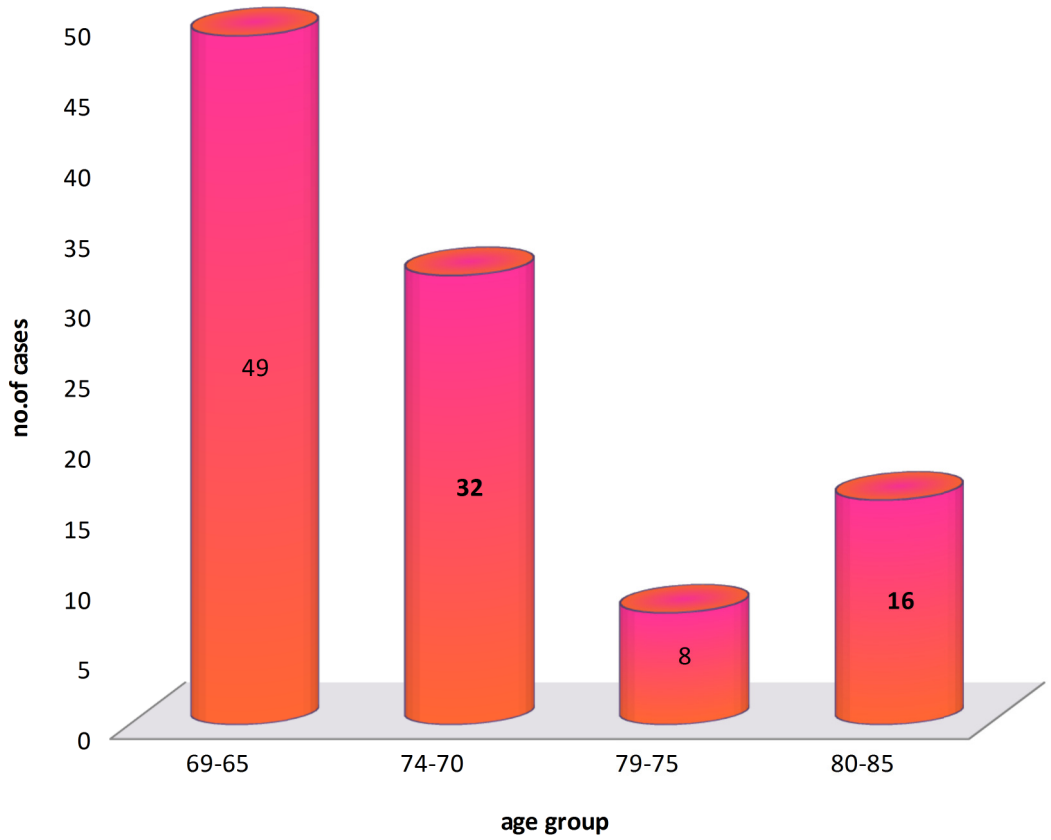


FIGURE 1

TABLE 2: GENDER DISTRIBUTION OF HOSPITALISED GERIATRIC PATIENTS

SEX	NO. OF PATIENTS	PERCENTAGE
Male	61	58.10%
Female	44	41.90%
Total	105	100%

A Total of 105 geriatric patients aged 65 yrs and above, and those who had satisfied the inclusion criteria were entrolled for the study. Table 1 shows that, of the total 105 geriatric patients enrolled in the study , 61 cases (58.10%) were males and 44 cases (41.90%) were females.

GENDER DISTRIBUTION OF HOSPITALISED GERIATRIC PATIENTS

FIGURE 2

TABLE 3: NUMBER OF DRUGS PRESCRIBED PER DAY PER PATIENTS

NO OF DRUGS PRESCRIBED PER DAY	NO OF PATIENTS RECEIVING DRUGS	PERCENTAGE OF TOTAL POPULATION
1	0	0
2	6	1.90
3	12	11.42
4	13	12.38
5	26	24.76
6	25	23.80
7	7	6.66
8	4	3.80
9	5	4.76
10	4	3.80
11	2	1.33
	Total =105	100%

From the data collected it was found that, of the total 105 patients enrolled in the study, 31patients were prescribed <5 medicines per day , 5-8 drugs were prescribed 63 patients and 11 patients were prescribed > 9 medicines per day figure3.

It was also found that the average number of drugs prescribed per day per patients was 5.71± 1.99(±SD). This result vary with a previous study conducted in which they found that the average number of drugs prescribed per patients was 5.8±2.1.

NUMBER OF DRUGS PRESCRIBED PER DAY PER PATIENTS

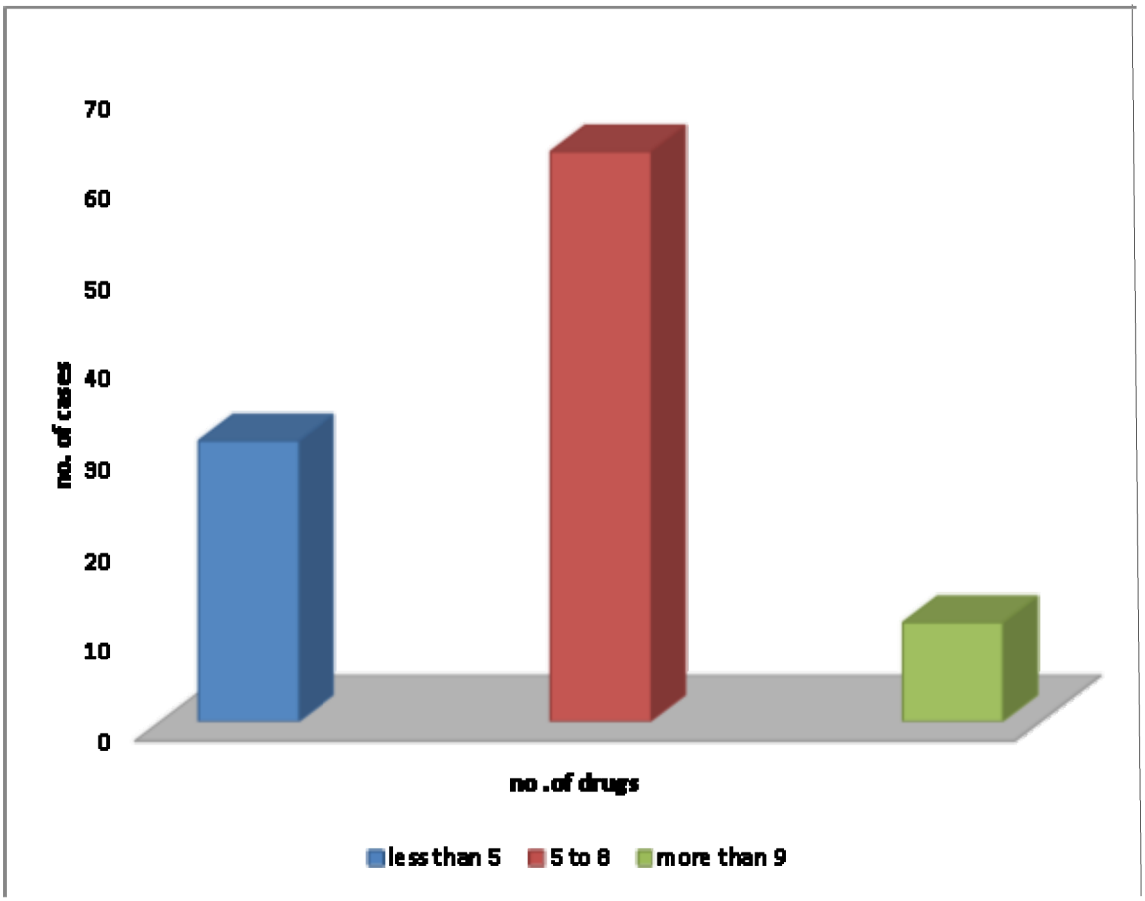


FIGURE 3.

TABLE 4: THE MOST COMMON DIAGNOSIS OF HOSPITALIZED GERIATRIC PATIENTS

DISEASE	CASES
Cardiovascular	18
Cerebrovascular disease	5
Diabetes	4
Respiratory disease	5
Infectious disease	4
Gastrointestinal disease	3
Musculoskel disorders	3
Vitamins	3

Table 4 shows that geriatric patients were commonly diagnosed with cardiovascular disease (18 cases), followed by cerebrovascular disease (5cases),Diabetes (1cases) , respiratory disease (4 cases),infectious disease (5cases), gastrointestinal disease (4cases), musculo- skeletal disorder (3cases) and vitamins (3cases)

THE MOST COMMON DIAGNOSIS OF HOSPITALIZED GERIATRIC PATIENTS

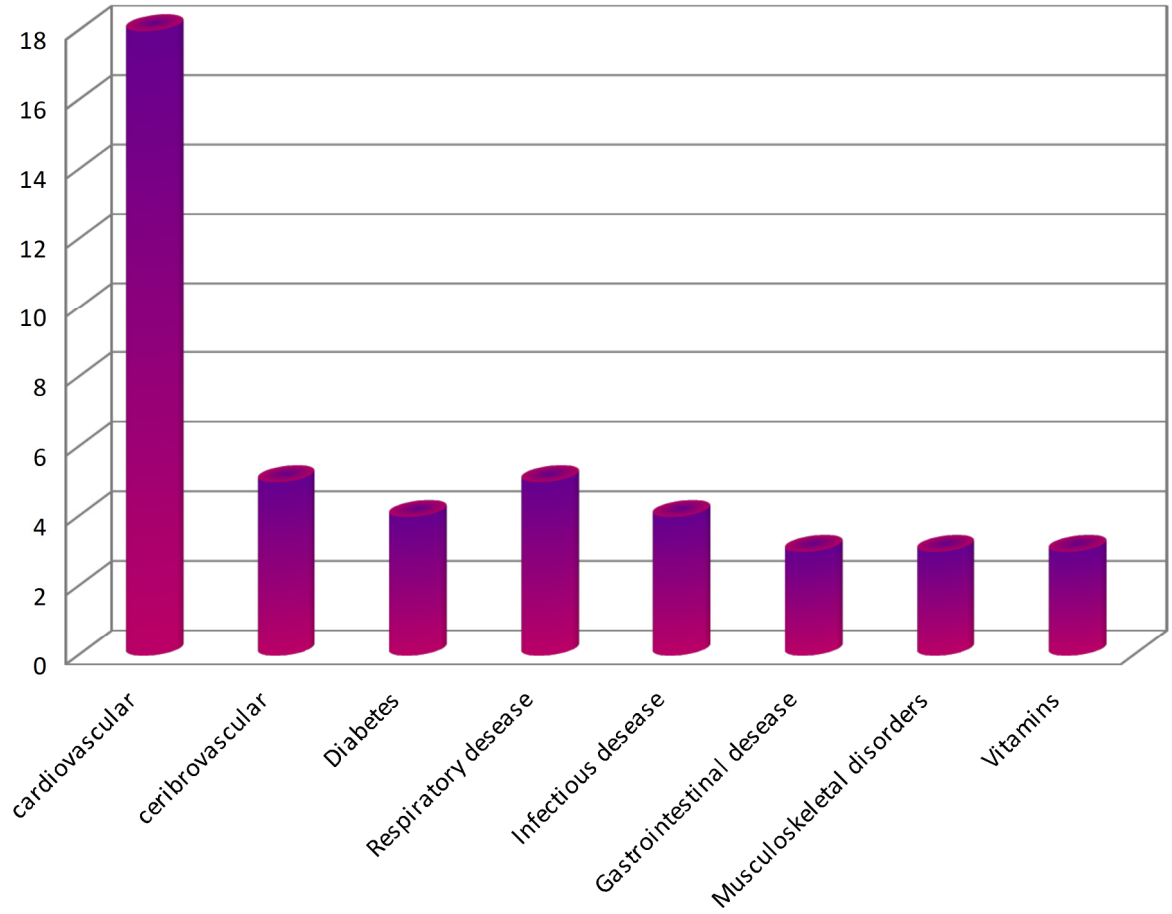


FIGURE 4

TABLE 5: DISTRIBUTION OF NUMBER OF MEDICATION PRESCRIBED AMONG HOSPITALISED GERIATRIC PATIENTS

SL NO	CLASS OF DRUGS	NO.OF DRUGS	PERCENTAGE
1	Cardiovascular and haemopoetic system	98	18.91

2	Vitamins and minerals	23	4.44
3	Gastrointestinal and hepatobilary system	102	19.69
4	Antibiotics	66	12.74
5	Respiratory system	59	11.38
6	Endocrine and metabolic system	87	16.79
7	Analgesics and NSAIDs	41	7.91
8	Central nervous system	26	5.01
9	Corticosteroid hormones	16	3.08
		Total= 518	100%

Table 5 indicates that gastrointestinal and hepatobiliary system drugs were the most prescribed drugs for geriatric patients (19.69%), followed by cardiovascular system drugs(18.91%), drugs for endocrine and metabolic system (16.79%)Antibiotics (12.74%), Respiratory system drugs (11.38%),Analgesics and NSAIDs (7.91%), drugs for central nervous system (5.01%) ,vitamins and minerals (4.44%), Corticosteroid hormones (3.08%). Many studies have documented the most commonly prescribed class of medications used by elderly patients was cardiovascular system drugs.

DISTRIBUTION OF NUMBER OF MEDICATION PRESCRIBED AMONG HOSPITALISED GERIATRIC PATIENTS

FIGURE 5

TABLE 6: NO. OF MEDICATION VS NO.OF DDIS

NO OF DRUGS	NO. OF PATIENTS	NO. OF POTENTIAL DDIS	PERCENTAGE
0-2	6	1	2.32

3-4	25	9	18.62
5-6	51	26	60.46
7-8	11	2	4.65
9-10	9	4	9.30
11-12	3	2	4.65
	Total =105	Total= 43	100

A total of 43 DDIs were detected in the study. Every geriatric patient had consumed more than 2 drugs per day and the patients were prescribed upto 11 drugs per day. From the data obtained from the prescriptions the patients and the data obtained using multidrug interaction checker- Medscape.

It was found that the average number of potential drug –drug interactions per patient was .5±.79. In a previous study conducted, the average number of DDIs per patient was found to be 1.38.

NO. OF MEDICATION VS NO. OF DDIS

FIGURE 6

TABLE 7: CLASSIFICATION OF DDIS

TYPE	NO. OF DDIS	PERCENTAGE
Pharmacokinetic	18	41.86
Pharmacodynamic	16	37.20
Unknown	9	20.93
	Total=43	100

Based on the mechanism, interactions were classified as pharmacokinetic, pharmacodynamic and unknown. A total of 43 interactions were identified in the study. Of that 18 DDIs (41.86%) were due to pharmacokinetic interactions, 16 DDIs (37.20%) were due to pharmacodynamic interactions and for 9 DDIs (20.93%) were unknown.

CLASSIFICATION OF DDIS

FIGURE 7.

TABLE 8: GENDER DISTRIBUTION OF DRUG –DRUG INTERACTIONS

SEX	NUMBER OF PATIENTS WITH POTENTIAL DDI	NUMBER OF PATIENTS ENROLLED	PERCENTAGE
Male	20	61	32.78%
Female	11	44	25%
Total	31	105	29.52%

Table and figure 8 shows that, of the total 61 males included in the study 22patients (32.78%) was prescribed with medicines causing DDIs and of the 44 females enrolled in the study 19 patients (25%) were prescribed with medications to cause drug drug interactions. And 29.5% of total population were prescribed with medications causing DDIs.

GENDER DISTRIBUTION OF DRUG DRUG INTERACTIONS

TABLE NO 9 :DETAILS OF PHARMACOKINETIC INTERACTIONS OBSERVED:

SL NO	DRUG INTERACTION	TYPE OF REACTION	MECHANISM	MODIFICATION
1.	RANITIDINE-METRONIDAZOLE	Pharmacokinetic	Ranitidine reduces the absorption of Metronidazole	Omeprazole was suggested instead of Ranitidine

2	LOPERAMIDE-THEOPHYLLINE	Pharmacokinetic	Loperamide delays the absorption of theophylline	Should not be administered together
3	ALLOPURINOL-CLOPROPAMIDE	pharmacokinetic	Allopurinol increases the half life of Clopropamide	Decrease the dose of Allopurinol
4	RANITIDINE-KETOCONAZOLE	Pharmacokinetic	Ranitidine reduces the absorption of ketoconazole	Proton pump inhibitors to be used insted of ranitidine
5	CIPROFLOXACIN-DIAZEPAM	Pharmacokinetic	Ciprofloxacin increases the level of diazepam	Norfloxacin to be used instead of Ciprofloxacin
6	METOPROLOL-THEOPHYLLINE	Pharmacokinetic	Metoprolol decreases theophylline metabolism	Dose adjustment-theophylline dose to be reduced
7	METOCLOPRAMIDE-DIGOXIN	Pharmacokinetic	Metoclopramide reduces digoxin absorption	Promethazine suggested instead of metoclopramide
8	ASPIRIN – METHYLPREDNISOLONE	pharmacokinetic	Methyl prednisolone stimulats liver metabolisam of aspirin & increases renal eliminations	Moniter aspirin concentration when adding methyl prednisolone
9	METOCLOPRAMIDE-PARACETAMOL	Pharmacokinetic	Metoclopramide increase the rate of absorption of paracetamol	Promethazine to be used instead of metoclopramide
10	WARFARIN-RIFAMPICIN	Pharmacokinetic	Increase hepatic microsomal enzyme metabolisam of warfarin by rifampicin	Rifampin are discontinued to avoid excessive bleeding
11	SIMVASTATIN-DIGOXIN	Pharmacokinetic	Simvastatin increases the serum level of Digoxin	Should not be administered together

TABLE NO:10 DETAILS OF PHARMACODYNAMIC INTERACTIONS OBSERVED:

SL N	DRUG INTERACTION	TYPE OF REACTION	MECHANISM	MODIFICATION

O				
1	ENALAPRIL-SPIRANOLACTONE	Pharmcodynamic	Pharmacodynamic synergism,Risk of hyperkalemia	Frusamide suggested instead of Spiranolactone
2	ENALAPRIL- GLIMPRIDE	Pharmacodynamic	Enalapril increases the effects of glimipride	Should not be administered together
3	OMEPRAZOLE- LOSARTAN	Pharmacodynamic	Omeprazole descreases effects of losartan	Should not be administered together
4	RIFAMPICIN-THEOPHYLLINE	Pharmacodynamic	Rifampicin reduces theophylline effect	Should not be administered together
5	HYDROCHLOROTHIAZIDE-ACARBOSE	Pharmacodynamic	Hydrochlorothiazide decrease the effects of acarbose	Frusemide was used instead of Hydrochlorothiazide
6	CLARITHROMYCIN-CLOPIDOGREAL	Pharmacodynamic	Clarithromycin decreases the level or effects of clopidogrel by affecting hepatic metabolisam	Should not be administered together
7	NIFEDIPINE-CLOPIDOGREL	Pharmacodynamic	Nifedipine will decrease the level or effect of clopidogrel by affecting hepatic intestinal enzyme CYP 3A4 metabolisam	Should not administered together
8	PHENYTOIN-AZITHROMYCIN	Pharmacodynamic	Phenytoin will descrease azithromycin level	Should not administered together
9	NIFEDIPINE-ATORVASTATIN	Pharmacodynamic	Nifedipine will increase the effect atorvastatin by affecting hepatic enzyme CYP3A4 metabolisam	Should not administered together
10	PANTOPRAZOLE-CLOBAZAM	Pharmacodynamic	Pantoprazole will increase the effectof clobazam	Dose adjustment may be required
11	VITAMIN E- WARFARIN	Pharmacodynamic	Vitamin e enhance anticoagulant effects of warfarin	Vitamin E dose will be reduced

12	PHENOBARBITAL-CLOPIDOGREL	Pharmacodynamic	Phenobarbital increase in antiplatelet effects of clopidogrel	Clopidogrel dose will be redused
13	DICLOFENAC- ASPIRIN	Pharmacodynamic	Aspirin and diclofenac both increase anticoagulation	Should not be administered together
14	CIPROFLOXACIN – PROPRANOLOL	Pharmacodynamic	Ciprofloxacin increases the effects of propranolol	Propranolol dose will be adjusted
15	AMOXICILLIN – WARFARIN	Pharmacodynamic	Amoxicillin increases effects of warfarin	Should not be administered together
16	ZAFILUKAST-THEOPHYLLINE	Pharmacodynamic	Zafilukast will increase the level or effect of theophylline by affecting hepatic /intestinal enzyme CYP3A4 metabolisam	Concurrent administration should be avoided
17	ATORVASTATIN-BUDESONIDE	Pharmacodynamic	Atorvastatin increase the effect of glycoprotein	Concurrent administration should be avoided

TABLE NO:11 DETAILS OF MISCELLANEOUS INTERACTIONS OBSERVED

1	METFORMIN-FUROSEMIDE	Un known	Metformin descreases levels of furosamide by unspecified interaction mechanisam	Should not be administered together
2	CALCIUM CARBONATE-ATENOLOL	Unknown	Calcium carbonate descreases effects of atenolol by unspecified interaction mechanisam	Should not be administered together
3	GLIMEPIRIDE-DICLOFENAC	Unknown	Diclofenac increases effects of glimepiride by unknown mechanisam	Should not be administered at same time

TABLE 12: FREQUENCY OF DRUGDRUG INTERACTION

FREQUENCY OF DRUG-DRUG INTRACTION	NO.OF CASES	PERCENTAGE

No.interaction	74	70.47
1	0	0
2	1	0.95
3	3	2.85
4	6	5.71
5	9	8.57
6	8	7.61
7	1	0.95
8	0	0
9	1	0.95
10	1	0.95
11	1	0.95
	105	100

74 (70.47%) cases did not had any combination of medicines to cause DDIs. The results were comparable to a previous study, in which , of a total of 100 patients taken for the study, 74 cases did not had any incidences of DDIs.

FREQUENCY OF DRUG DRUG INTERACTION

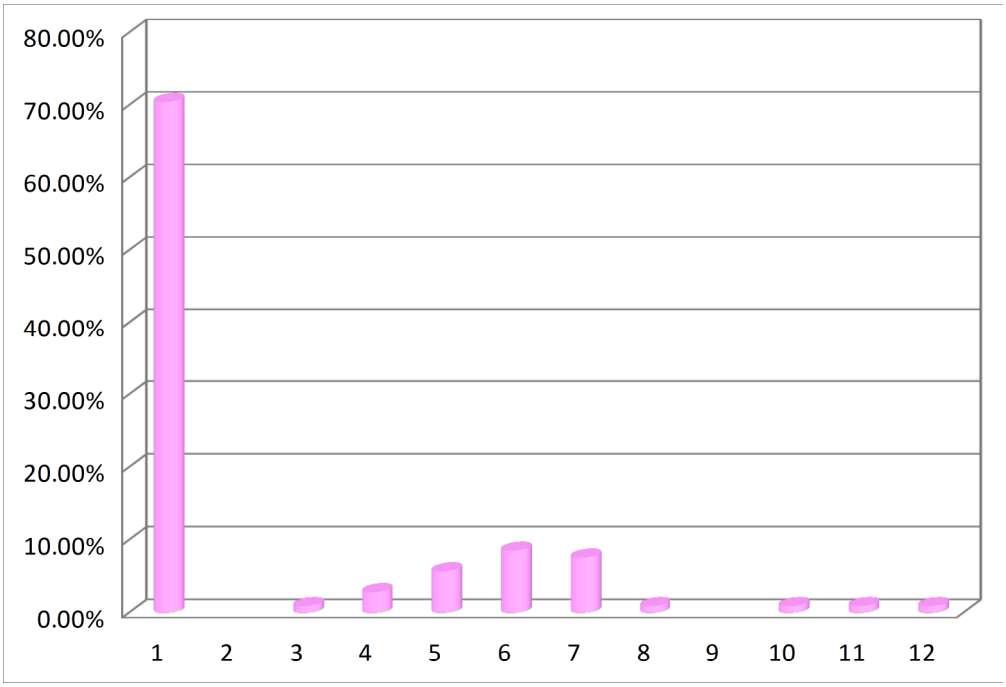


FIGURE 9

TABLE 13: ACTIVE SUBSTANCES MOST FREQUENTLY INVOLVED IN DRUGDRUG INTERACTIONS

SL NO	ACTIVE SUBSTANCE	NUMBER OF DDIS
1	Ranitidine	1
2	Loperamide	3
3	Allopurinol	1

4	Hydrochlorthiazide	1
5	Rifampicin	1
6	Omeprazole	1
7	Simvastatin	1
8	Metoprolol	1
9	Enalapril	2
10	Ciiprofloxacin	3
11	Diclofenac	2
12	Clopidogrel	4
13	Aceclofenac	1
14	Warfarin	2
15	Zafirlukast	1
16	Phenytoin	1
17	Prednesolone	1
18	Atenolol	1
19	Aspirin	2
20	Amoxycillin	2
21	Metoclopramide	1
22	Nefidipine	1
23	Atorvastatin	3
24	Metronidazole	1
25	Calcim carbonate	1
26	Phenobarbitone	1
27	Furosemide	1
28	Metformin	1
29	Heparin	1
30	Vitamin E	1
31	pantoprazole	1

Table 10 shows the ten active substances most frequently involved in potential DDIs in the study. Several cardiovascular drugs were the most frequently involved (clopidogrel, low dose aspirin, Heparin, Atorvastatin ,Enalapril, Diltiazem), followed by ciprofloxacin, CNS drug (phenytoin), gastrointestinal (pantoprazole), insulin and theophylline. Elderly patients are the population at the highest risk of potentialDDIs.They frequently take many drugs (polypharmacy), have several co- morbidities, and might not maintain adequate nutritional status. The application of evidence based medicine tends to increase the number of drugs prescribed to treat one disorder. Additionally, age related changes in pharmacokinetics and pharmacodynamic characteristics, including impairment in many organ functions (particularly kidney and liver) increase the complexity of drug interactions in elderly people.

ACTIVE SUBSTANCES MOST FREQUENTLY INVOLVED IN DRUG DRUG INTERACTIONS

FIGURE 10.

TABLE 14:COMBINATION OF DRUGS MOST COMMONLY INVOLVED IN DDIS

SL NO.	DRUG COMBINATION	SEVERITY	NO OF INTERACTIONS
1	Clopidogrel- Atorvastatin	Moderate	21
2	Clopidogral- Heparin	Moderate	17
3	Heparin- Aspirin	Moderate	12
4	Clopidogrel- pantoprazole	Major	11
5	Iron- Mg/Al/Ca	Moderate	8
6	Ciprofloxacin- Insulin	Moderate	6
7	Atorvastatin- Diltiazem	Moderate	6
8	Clopidogrel- Omeprazole	Major	5
9	Phenytoin-Folic acid	Moderate	5
10	Phenytoin-Thenophylline	Moderate	4

Clopidogrel-Atorvastatin was the most frequently involved drug combination causing DDIs(21 cases), followed by Clopidogrel-Heparin (17 cases), Heparin-Aspirin(12cases), Clopidoggrel-Pantoprazole(11cases), Iron-Mg/Al/Ca(8cases), Ciprofloxacin- Insulin(6 cases),Atorvastatin- Diltiazem (6cases), Clopidogrel-Omeprazole(5cases), Phenytoin – Theophylline (4cases).

TABLE 15: NUMBER OF DRUGS VS DRUG – DRUG INTERACTION YES/ NO CROSS TABULATION

NO.OF DRUGS	POTENTIAL DRUG DRUGINTERACTION		TOTAL
	YES	NO	
Upto 5 drugs	20 (33.33%)	40 (54.05%)	60(57.14%)
6-8 drugs	8 (13.33%)	16 (21.62%)	24(22.85%)
9-11 drugs	3(14.28%)	18 (24%)	21(20%)
Total	31	74	105(100%)

Table clearly indicates that, as the number of drugs prescribed to the patient increases, the percentage of number of cases of potential of DDIs also increases. This increasing trend of DDIs with increase in the number of medication . A previous study conducted also indicated a positive relationship between the number of drugs and number of drugs and number of drug drug interactions.

NUMBER OF DRUGS VS DRUG DRUG INTERACTION YES /NO CROSS TABULATION

FIGURE 11.

DISCUSSION

- A total of 105 geriatric patients were included in the study. Of which, 58.10% were males and 41.90% were females.
- From the study, it was found that, the average age of the study group was 73.65± 5.77yrs. In male gender, the average age was found to be 74.16±5.86 yrs, and the average age of the female gender was found to be 72.93 ± 5.60yrs.
- From the data collected from the case sheet of the patients, most of the patient consumed more than 4 drugs per day and the average number of drugs consumed per day per patient was found to be 5.8 ± 2.1.
- The most common diagnosis of hospitalised geriatric patients was cardiovascular diseases, followed by cerebrovascular diseases, Endocrine disease (especially diabetes), Respiratory diseases, infectious disease and gastrointestinal disorders.
- The gastrointestinal and hepatobiliary system drugs were the most prescribed drugs for geriatric patients (19.69%), followed by cardiovascular system drugs(18.91%), drugs for endocrine and metabolic system (16.79%)Antibiotics (12.74%), Respiratory system drugs (11.38%),Analgesics and NSAIDs (7.91%), drugs for central nervous system (5.01%) ,vitamins and minerals (4.44%), Corticosteroid hormones (3.08%). Many studies have documented the most commonly prescribed class of medications used by elderly patients was cardiovascular system drugs.
- A total of 43 DDIs were detected in the study and the average number of potential drug drug interactions per patient was found to be .5±7.9(±SD). It was also found that, 74 case did not have any combination of medicines to cause potential DDIs.
- Of a total of 43 potential DDIs detected in the study, 41.86% were due to pharmacokinetic interaction between the drugs, 37.20% were due to pharmacodynamic interaction between the drugs and for the remaining cases (20.93%), the reason for the interaction was unknown.
- Of a total of 61 males included in the study, 20 males had drugs causing potential DDIs (32.78) and of the 44 females included in the study, 19 females had drugs causing potential DDIs (25%).

- The active substances most frequently involved in DDIs were Cardiovascular drugs (clopidogrel, low dose Aspirin, Heparin, Atorvastatin, Enalapril, Diltiazem), followed by ciprofloxacin, CNS drug (phenytoin), gastrointestinal (pantoprazole),Insulin and Theophylline.The combination of Clopidogrel Atorvastatin caused the most number of DDIs, followed by Clopidogrel Heparin, Heparin Aspirin and Clopidogrel pantoprazole.
- The combination of Clopidogrel, pantoprazole and Clopidogrel omeprazole were the most severe DDIs (Major) detected in the study.

CONCLUSION

The incidence of DDIs in hospitalized geriatric patients was substantial. The number of DDIs do not depend only on the number of drugs prescribed, it also depend on the combination of drugs prescribed which has the potential to cause interaction and other factors include the age related changes in the pharmacokinetics and pharmacodynamic characteristics of the elderly patient. To reduce DDIs, the number of medications for the geriatric patients should be properly controlled and it is recommended to eliminate all medications without therapeutic benefit, goal or indication. Beside, pharmacist should increase their role in managing medication therapy through collaboration with other health care professionals to prevent and resolve drug drug interaction problem.

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